CLAIMS

1. A method of preparing the chiral (±) isomers of indole-2,3-dione-3-oxime derivatives (Compounds A or B), which method comprises the subsequent steps of

(i) Reacting an 8-amino-1,2,3,4-tetrahydro-isoquinoline (Compound 9) derivative with chloral hydrate and hydroxylamine hydrochloride to give an *N*-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-2-hydroxyimino-acetamide (Compound 10) derivative (Step 9);

(ii) Adding sulphuric acid to the *N*-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-2-hydroxyimino-acetamide (Compound 10) derivative obtained in step (i) (Step 10); and

(iii) Reacting the 2,3-dioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-h]isoquinoline (Compound 11) derivative obtained in step (ii) with chiral (enantiopure (*R*) or (*S*)) α-*N,N*-diBoc-aminoxy-γ-butyrolactone to obtain the desired chiral end product, i.e. enantiopure (R)- or (S)-2-[2-oxo-1,2,6,7,8,9-hexahydro-pyrrolo[3,2-h]isoquinolin-3-ylideneaminooxy]-4-hydroxy-butyric acid) (Compound A or B) (Step 11);

followed by recovery of the desired end product.

2. The method of claim 1, which method further comprises the step of

(a) reacting enantiopure (*S*) or (*R*) α-hydroxy-γ-butyrolactone with *N,N*-diBoc-hydroxylamine to give enantiopure (*S*) or (*R*) α-*N,N*-diBoc-aminoxy-γ-butyrolactone (Step 8a);

followed by steps (i) to (iii) of claim 1.

3. The method of claim 2, which method further comprises the step of

(b) subjecting *N,N*-diBoc-*O*-benzylhydroxylamine to hydrogenation to give *N,N*-diBoc-hydroxylamine (Step 7);

followed by step (a) of claim 2, and steps (i) to (iii) of claim 1.

4. The method of claim 3, which method further comprises the step of

(c) converting *O*-benzylhydroxylamine into *N,N*-diBoc-*O*-benzylhydroxylamine using Boc_2O (Step 6);

followed by step (b) of claim 3, step (a) of claim 2, and steps (i) to (iii) of claim 1.

5. The method of claim 1, which method further comprises the step of

(d) reacting enantiopure (*S*) or (*R*) α-hydroxy-γ-butyrolactone with tosyl chloride to give enantiopure (*S*) or (*R*) α-tosyloxy-γ-butyrolactone (Step 5);

followed by step (c) of claim 4, step (b) of claim 3, step (a) of claim 2, and steps (i) to (iii) of claim 1.

6. The method of any of claims 1-5, wherein

the 8-amino-1,2,3,4-tetrahydro-isoquinoline (Compound 9) derivative of step (i) is 4-(8-amino-2-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-*N,N*-dimethyl-benzenesulfonamide (to obtain *N*-[5-(4-dimethylsulfamoyl-phenyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-yl]-2-hydroxyimino-acetamide); and

the 2,3-dioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-h]isoquinoline (Compound 11) derivative of step (iii) is *N,N*-dimethyl-4-(8-methyl-2,3-dioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-h]isoquinolin-5-yl)-benzenesulfonamide;

giving enantiopure (R)- or (S)-2-[5-(4-dimethylsulfamoyl-phenyl)-8-methyl-2-oxo-1,2,6,7,8,9-hexahydro-pyrrolo[3,2-h]isoquinolin-3-ylideneaminooxy]-4-hydroxy-butyric acid as the end product (Compound A or B).

7. A method of preparing a starting material for use according to the method of claims 1-6, which method comprises the subsequent steps of

(i) acetylating a racemic mixture of α-hydroxy-γ-butyrolactone to obtain racemic α-acetoxy-γ-butyrolactone (Step 1);

(ii) subjecting the racemic α-acetoxy-γ-butyrolactone obtained in step (i) to enzymatic de-acetylation to obtain enantiopure (*S*) or (*R*) α-acetoxy-γ-butyrolactone (Step 2); and

(iii) subjecting the enantiopure (*S*) or (*R*) α-acetoxy-γ-butyrolactone obtained in step (ii) to hydrolysis using acidic ion-exchange (Step 3);

followed by recovery of the desired end product.

8. The method of claim 7, which method further comprises the step of

(iv) subjecting the enantio-impure remainings of step (iii), i.e. the enantio-impure α-hydroxy-γ-butyrolactone and α-acetoxy-γ-butyrolactone, to racemisation using acid or base;

followed by re-entry of the racemic mixture into step (i).

9. The method of claim 7, wherein the enzymatic de-acetylation of step (ii) is carried out using a lipolytic enzyme.